



Master in Innovation Economics and Management

BIG DATA IN HEALTHCARE:

Real World Evidence in price and reimbursement

Juliette Monpays

Tutor:

Professor Argentino Pessoa

September 2017

Biographic Note

Juliette Monpays was born in France in 1993. She completed her licence degree in Economy and Management in Lille, (France) with a one-year Erasmus programme in Valencia (Spain). Then she moved to Porto (Portugal) to enrol the Master Degree in Innovation Economics and Management of the Faculdade de Economia do Porto (FEP).

She did a six-month internship in Hamburg (Germany) in Young and Rubicam, an advertisement agency. One of the client of the agency was Sanofi, a top-5 pharmaceutical company. She developed a growing interest for this area and decided therefore to intern in Sanofi in the Market Access division where she learned about global strategy in price and reimbursement of drugs.

She now interns at the GSK company in the Key Accounts Management division, learning about pharmacies sales strategy in vaccines and respiratory drugs.

Acknowledgement

I wish to express my sincere gratitude to my tutor Argentino Pessoa who gave me preciousness advices throughout the whole year.

I also want to thank all the teachers of my Master degree in Innovation Economics and Management for their teaching and a big thank you to all the students. I will always remember the warm welcome they gave me despite the cultural differences and my terrible accent. I particularly want to express my gratitude to André Luis Quintino Principe, my “Portuguese teacher”, who helped me in every moment I was lost. I honestly think that almost half of my Portuguese vocabulary comes from him.

Finally, I wish to express my gratitude to my university, Faculdade de Economia do Porto, which gave me the wonderful opportunity to study in a Portuguese Master Degree. It was a truly amazing experience that I will never forget.

Abstract

This paper focuses on the positive impact of Real World Evidence (RWE) in Health Technology Assessment (HTA) submissions where price and reimbursement of drugs are informed. These last years, literature on RWE have proportionally increased with the phenomenon. Opinions in the literature and in pharmaceutical industries are mostly very enthusiastic; sometimes affirming that RWE could change a negative HTA decision into a positive one. Nevertheless, I doubt very much that RWE, a very new phenomenon, has a such strong impact. I'm sure RWE does make a positive impact on HTA decisions, but this impact seems to be restricted. This paper's intention is to bring to the actual literature a more detailed picture of the true impact of RWE in HTA decisions.

The development of this dissertation is based on two types of studies. The first one is a quantitative study on the acceptance of RWE in HTA decisions which objective is to analyse HTA submissions to understand how often RWE are refused and collect the reasons of their refusal. In the second study, I focus on three international cases where the reimbursement of a drug was first refused but, in re-submissions with an additional RWE, a positive reimbursement decision was given. The cases are the following: Yervoy in Australia HTA (PBAC), Zaltrap in Scotland (SMC) and Myozyme in France (HAS).

The main findings of my research confirm that RWE is not overcoming Randomized Controlled Trials (RCTs). RWE is often refused in price and reimbursement submissions. Reasons expressed by HTA are all links to the lack of rigor of RWE. Nevertheless, the three case studies suggest that RWE has a stronger impact in re-submission when RCTs failed to bring evidences. Its impact has been confirmed in market access with Managed Entry Agreements (MEA), long-term follow up and in weak economic case. But its impact is restricted, in that the RWE never changed only by itself the HTA decision, but always in combination with a discount, an MEA or a RCT. While the role of RWE is very often described in the literature as a support to RCTs, I would rather conclude that its main impactful role is to fill the "evidence gap" when RCTs failed to bring it.

Keywords: Real World Evidence (RWE), Health Technology Assessment (HTA), Randomized Controlled Trials (RCTs), Big Data, Zaltrap, Yervoy, Myozyme

JEL Codes: H51; I18

Resumo

Esta dissertação aborda o impacto positivo da Real World Evidence (RWE) nas submissões Health Technology Assessment (HTA), que contêm informações relativas ao preço e reembolso dos fármacos. Nos últimos anos, a literatura sobre RWE aumentou proporcionalmente ao fenómeno. As opiniões na literatura e na indústria farmacêutica são geralmente muito otimistas: por vezes, uma RWE pode reverter uma decisão negativa de uma HTA em decisão positiva. Todavia, duvida-se que a RWE, um fenómeno recente, possa ter um impacto tão forte. A RWE tem um impacto sobre as decisões de HTA, mas este impacto parece ser limitado. O objetivo desta dissertação é alargar o conhecimento da literatura atual com uma visão mais detalhada do impacto da RWE nas decisões das HTA.

O desenvolvimento desta dissertação assenta em dois tipos de estudo. O primeiro é um estudo quantitativo sobre a aceitação da RWE pelas HTA; cuja metodologia possibilita analisar decisões HTA para avaliar com que frequência as RWE são rejeitadas e indicar as razões da rejeição. No segundo estudo, o foco incide sobre três casos internacionais onde o preço e reembolso dos fármacos foram inicialmente rejeitados, mas com nova submissão (“re-submissão”), e com uma RWE suplementar, foi dada uma decisão positiva de reembolso. Os casos escolhidos foram os seguintes: Yervoy na Austrália HTA (PBAC), Zaltrap na Escócia (SMC) e Myozyme na França (HAS).

Os principais resultados do presente estudo confirmam que a RWE não supera os Randomized Controlled Trials (RCTs). A RWE é frequentemente rejeitada nas submissões de preços e reembolsos. As razões apresentadas pelas HTA apontam para uma falta de rigor da RWE. No entanto, os três casos sugerem que a RWE tem um impacto mais importante nas “re-submissões” quando os RCTs falham na obtenção de provas. O seu impacto foi confirmado no acesso ao Mercado com os Managed Entry Agreements (MEA), no longo prazo e em casos económicos fracos. No entanto, o seu impacto é sempre limitado, uma vez que a RWE nunca alterou por si só uma decisão da HTA, exceto em combinação com um desconto, um MEA ou um RCT. Ao passo que a função da RWE é frequentemente descrita na literatura como um apoio às RCTs, neste estudo conclui-se que a sua principal função é preencher a lacuna de provas quando o RCT foi ineficiente nesse sentido.

List of contents

Biographic Note.....	I
Acknowledgement	II
Abstract	III
Resumo	IV
List of contents.....	V
List of tables and figures	VI
List of abbreviations	VII
Introduction	1
Review of the literature	4
Efficacy vs Effectiveness vs Efficiency	4
RCTs and RWE : Two different concepts	5
Innovation	6
Real World Evidence Typology	7
Typology by sources	7
Typology by approach	9
Advantages and Drawbacks of RWE comparing to RCTs	10
The present use of RWE	13
Managed Entry Agreements	15
Methodology	17
Objective	17
Selection criteria and Methodology.....	17
Collection of Data.....	18
Quantitative Study on RWE Acceptation.....	19
Qualitative Study : Case Study	25
Brief of the case	26
Explanation of the QALY system	27
Explanation of the SMR/ASMR system	28
Case 1: Yervoy Australia	29
Case 2 : Zaltrap Scotland	34
Case 3 : Myozyme France.....	38
Conclusion.....	45
References	47

List of tables

Table 2.1: RCTs VS RWE distinct features	5
Table 2.2: Main differences between Retrospective and Prospective study	5
Table 4.1: HAS Decisions in January 2017	5
Table 4.2: Cases from Table 1 with RWE	5
Table 4.3: Acceptation of the RWE according to the Efficacy and Tolerance category of evidence	22
Table 4.4: Misodel and Entresto specific cases	23
Table 5.1: Main info on the three cases chosen	26
Table 5.2: QALY gain and cost difference between the submission and the resubmission	36
Table 5.3: Key elements which changed the HTA decision.....	42

List of figures

Figure 2.1: Prospective and Retrospective Studies	9
Figure 2.2: Sum up of the advantages and drawbacks of RCTs and RWE	5
Figure 2.3: Evidence needs evolves over time	5
Figure 4.1: Percentage of submissions with RWE	20
Figure 4.2: Proportion of submissions accepted or refused per the presence of RWE	20

List of abbreviations

ASMR: Amélioration du Service Médical Rendu (Improvement of the Medical Benefits)

EAS : Expanded Access Program

FDA : U.S Food & Drug Administration

HAS: Haute Autorité de Santé (French HTA)

HTA: Health Technology Assessment

INAHTA: International Network of Agencies for Health Technology Assessment

INN: International Non-proprietary Name

irAES: Immune Related Adverse Events

MEA: Managed Entry Agreements

PBAC: Pharmaceutical Benefits Advisory Committee (Australian HTA)

PROs: Patient Reported Outcomes

QALY: Quality-Adjusted Life Year

RCTs: Randomized Controlled Trials

RWE: Real World Evidence

SMC: Scottish Medicines Consortium (Scottish HTA)

SMR: Service Médical Rendu (Medical Benefits)

1. Introduction

The last decades have seen huge advance and modification of data collection and use in our societies and the healthcare market hasn't been an exception, big data reworked deeply the area. Many decisions are now driven by data, from the R&D of new molecules to the pharmacovigilance after the release of a drug. Traditionally, the RCTs (Randomized Controlled Trials) are granted as the highest collection data because they are designed to be unbiased and have less risk of systematic error (Burns et al, 2011). Nevertheless, even though RCTs remain the "gold standard" to obtain evidences, they have some limits. Indeed, the results are obtained in a highly controlled context and can be far from the reality. Innovation in technologies and the rise of Big Data enabled new ways of collecting data closer to the reality called Real World Evidence (RWE). In its Task Force Report of 2007, ISPOR described Real World Data as "data used for decision making that are not collected in conventional controlled randomized trials. While data are simply raw materials and alone are not informative, evidence is structured and aims to inform a conclusion or a judgment". According to this definition, Real World Evidence is the common term used while approaching the subject, therefore it is the term employed in this paper. RWE appeared in the last decade and is becoming slowly a greater factor in decision-making, especially in Health Technology Assessment (HTA) submissions where price and reimbursement of drugs are informed. Nowadays a significant proportion of price and reimbursement submissions of new drugs are composed of RWE.

These last years, literature and investigation on RWE have proportionally increased with the phenomenon. They are generally coming from institutions as the European Commission STAMP (Safe and Timely Access to Medicines for Patients) or the work of Garrison et al in the ISPOR Task Force (2007) which has been a good foundation for structuring this paper, indeed the International Society for Pharmaco-economics and Outcomes Research (ISPOR) is a great reference in health economics and outcomes research. Another important part of the literature found on RWE is coming from consulting companies of the area as IMSHealth or Deloitte. They have obviously, interest in telling how great RWE is, taking account, they are directly selling services linked to RWE. Articles found were very positive, assuring RWE could overtake RCTs. A glance

to some HTA decisions is nevertheless confirming the opposite, even though RWE represents a significant part of the evidences provided, it is always considered as a complement to RCT. Furthermore, many RWE are simply refused. Some other studies of RWE in HTA decisions exist but with very few case studies, and if they have, they are very light, describing in few lines the result of the price/reimbursement submission, and the RWE used: Harrison (2016) SVM Pharma report, IMS Brogan report (2013), Liden (2005) article in Pharmaphorum website.

In this context, this paper aims at analyzing recent HTA submissions in order to determine its real added value. This paper claims to answer the following question: *How Real World Evidence (RWE) can positively impact price and reimbursement of drugs?*

For answering this question the development of this dissertation is based on two types of studies. The first one is a quantitative study on the presence of RWE in HTA decisions and its acceptance. My hypothesis is that RWE is mainly refused because of its biased nature. The objective of this first study is to collect the reasons why RWE is often refused as evidence in HTA decisions. I decided to pick all submissions published on the French HTA website (HAS — Haute Autorité de Santé) of January 2017. The exclusion cases are the renewal submissions which are not interesting for our subject because of the reduced quantity of evidences needed and provided. Therefore, I include the inscriptions and revaluations of drugs.

In the second study, I focus on three international cases where a drug was not initially recommended but, in re-submissions with the addition of RWE, a positive reimbursement decision was given. These three cases are based on an article from the Pharmaphorum website (2015). This restricted amount of illustrations aims at deeply analyze each of them by providing a substantial background information of the drug before a deep study of the structure and value of the RWE used. The aim is to make a link between the two studies and understand why RWE is often refused and why some RWE, unlike the others, are accepted and are making a positive difference. The HTA submissions and results are all public and available on the HTA national respective website.

The rest of the study proceeds as follow: The second section reviews the literature by approaching the concept of RWE, its advantages and drawbacks compared to RCTs, and

its current uses. The third section explains the methodology of the quantitative RWE acceptance study and the three case studies, describing the criterion used for analyzing them. Section four is focused on the quantitative study of the French HTA decisions and RWE main reasons of refusal. Section five is dedicated to the case studies while the section six concludes this paper with suggestions on the future of RWE.

2. Real World Evidence (RWE)

2.1 Relevant concepts

2.1.1. Efficacy vs Effectiveness vs Efficiency

The work of Cochrane in 1971 in his book ‘Random reflections on health services’ imposed the base of nowadays health care services and showed the need of distinguishing three different concepts: efficacy, effectiveness, efficiency. These terms are now pillars of health drugs assessment:

Efficacy measures, in ideal circumstances, if the drug does more good than harm. It answers the following question: “Does it work?”

Effectiveness is assessing if the drug works in real circumstances, ‘Does it work in real?’

And finally, **efficiency** is counterbalancing results with the resources allocated ‘Does it worth it?’

Efficacy does not imply effectiveness. Let’s take as an example a drug with a very heavy treatment. The treatment requires ten injections per day and numerous pills. Injections and pills must be taken at very strict times; any differences of 15 minutes will decrease the effect of the drug by 50%. If all the criteria are respected, the drug is working perfectly and the illness will be stopped. On a clinical point of view, the efficacy of the drug is obvious but the effectiveness will be very low. In a clinical trial with a constant physician’s help and observation, patients will succeed to take fully the treatment. Back home and alone, patients won’t manage such a complex treatment.

Effectiveness does not imply efficiency. Imagine a treatment for eczema implying three hospital visits per year; physicians apply a specific cream, too dangerous for patients to do it alone. The treatment works perfectly but its cost and the resources needed are far too high. Multiply the number of hospital visits by the people suffering of eczema, the capacity of today hospitals won’t be enough. The effectiveness of the treatment is proven but it is not efficiency.

2.1.2 RCTs & RWE: two different concepts

A Randomized Control Trial (RCT) is “a trial in which subjects are randomly assigned to one of two groups: one, the experimental group, receiving the intervention that is being tested, and the other, the comparison group or control, receiving the conventional treatment” (Kendall, 2003). RCTs’ objective is to delete all possible bias in order to calculate the exact effect of an intervention. Sibbald (1998) in his paper “Understanding controlled trials: Why are randomized controlled trials important?” defines several important features that RCTs must respect to eliminate bias:

- Patients are randomly assigned to the groups
- Patients remain unaware of the assignment of the groups (Simple blinding) or patients **and** physicians remain unaware of the assignment of the groups (Double blinding)
- All groups are treated equal except for the given treatment

Randomization and blinding ensure that environment influence is reduced at its minima. Results are obtained in a highly controlled context, by nature RCTs are assessing **efficacy**. In opposition, Real World Evidence are evidences coming from data that are not collected in conventional Randomized Control Trials. Outside of this highly controlled context, RWE assess the drug in the “real world” measuring if the treatment is actually working in real condition, it is assessing **effectiveness**.

Table 2.1: RCTs VS RWE distinct features

	Randomized Control Trials	Real World Evidence
Answer the question	Does it work?	Does it work in real?
Primary Focus	Efficacy, safety and quality	Effectiveness
Type of trial	Experimental/Interventional	Observational/Non-interventional
Circumstances	Ideal circumstances	Real circumstances
Randomization &Blinding	Yes	No
Monitoring	Intense	Not required
Comparators	Gold standard/Placebo	None/Standard clinical practice
Patient Population	Narrow and Restricted	Wide and Unrestricted
Cost	€€€	€

Source: “Demonstrating Value with Real World Data: A practical guide”, May 2011, Association of the British Pharmaceutical Industry (ABPI)

2.2. Innovation

RWE is very new and its future is still unsure. Going through the literature there is a consensus to say RWE can be a big opportunity but its impact and role compared to RCTs is still unclear.

According to Schumpeter, the "gale of creative destruction" in "Capitalism, Socialism and Democracy" in 1942 describes the "process of industrial mutation that incessantly revolutionizes the economic structure from within, incessantly destroying the old one, incessantly creating a new one". RWE is changing the structure of the pharmaceutical industry but unlike breakout innovation it is growing very slowly and its impact is unclear. It is not clearly "destroying the old one".

- **Destruction creation:** RWE overcome RCTS

Some are very enthusiast and see RWE as the "new normal" (Sujay, 2017), "changing the game" (Thompson, 2017) "Investors [...] need to think about how these companies will shift from clinical evidence development to real-world evidence development in order to yield the expected return on investment."

- **Destruction Mutation:** RWE coexist in a complement way with RCTs

While other think that "The traditional role for RWD is to support RCT data" (Jónsson, April 2017).

"To evaluate the cost-efficiency of a drug in a real-world environment and gauge its impact on improving the quality of healthcare, RCTs need to be supplemented or followed up with the comparatively new standard, called real-world evidence (RWE)." (Saha et al, April 2015).

A new set of technology (Computer, wearable technology, cloud etc) is making easier the share of data from the real world, transforming the pharmaceutical industry.

Disruptive Innovation is described as the « Innovator Dilemma » by the professor Christensen; Disruptive technologies are "innovations that result in worse product performance, at least in the near term."

Actually, RWE is showing a great similarity to the innovator dilemma. RWE is not as better as RCTs. RCTs are still considered as the gold standard in the pharmaceutical industry but RWE could overtake it.

It seems that RWE is a kind of innovation that is working in “Snowball effect”: “The concept of a large user base implies that the value of a product or a service increases as the number of users, together with complementary goods or services, increase.”

(Goodman et al, 2013). Quantity is a key factor for the RWE network system works. More data are produced and exchanged, more evidences are available to prove drug’s efficacy or drug comparison. As a snowball, at the beginning the process is slow and then it is exponentially growing.

2.3 RWE Typology

2.3.1 Typology by data sources

ISPOR, in its Task Force on Real World Data in coverage and payment decisions, sums up six Real World Data sources:

- (1) **Supplement to RCTs**, also called Piggyback because they are not the reason why the trial has been conducted, are additional information collected alongside the RCT. They are frequently health economic data as quality of life information. It is a convenient way to collect more data without conducting another study but as the initial trial was not made for the purpose of collecting these “second lines” data, the design of the RCT can be incompatible. One of the most frequent critics found in the literature, for example O’Sullivan et al, in 2005 in their paper “Collection of Health-Economic Data Alongside Clinical Trials: Is There a Future for Piggyback Evaluations?”, is that piggyback data are not Real World Data as they are collected in a “false environment”. The behaviors of the patients can be far from the reality which is problematic since the objective of RWD is to get insights from the “real world”.
- (2) **Practical Clinical Trials or Large Sample Trials** are prospective studies with randomized assignment but with a bigger sample in a more heterogeneous

population (Tunis et al, 2003). The exclusion criteria are less strict, so the sample follows better the real-life settings. It is an efficient way to combine the data collection rigor of RCTs with the veracity of real world data. But, as the study is conducted in large sample and also in longer time it is very expensive. For example, the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), is the largest hypertension clinical trial ever conducted: a sample of 42 418 patients (33 357 patients stayed on their study drugs until the end of the study) with a mean follow-up of 4.9 year has cost 120 million dollars (Beevers, 2003).

- (3) **Patient Registry** is a “prospective method to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure” (Gliklich et al, 2007). Patient registries can be conducted by a wide range of public or private institutions as government, non-profit organization, hospitals, private company etc. For example, the Cystic Fibrosis Patient Registry has been created in 1966 and is collecting data on health outcomes, clinical care and demographic characteristics. It has nowadays data about 28,000 people with Cystic Fibrosis on decades (Cystic Fibrosis Foundation Website).
- (4) **Claims databases** are administrative data coming from health insurance programs and health care providers as bills. It is very useful data for knowing more on the quantity of care, their costs and reimbursements.
- (5) **Health Surveys** are good ways to obtain Patient Reported Outcomes. Patient Reported Outcomes (PROs) are defined as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else."(US FDA, 2009). PROs can be collected by questionnaire or direct interviews. Commonly PROs questionnaires and interviews collect information as Quality of Life, symptoms, health perceptions, ratings of healthcare.

(6) **Electronic health records (EHRs) and medical chart review.** Electronic Health Record (EHR) is defined as “a longitudinal collection of electronic health information about individual patients and populations” (Gunter et al, 2005). The objective of EHR is to have a structured format to be easily shared with other Health care organizations. Each organization adding its own information, EHR contain information from all medical professionals involved in a patient’s care. While Patient Registries provide information on a specific population, EHR provides long term and global information.

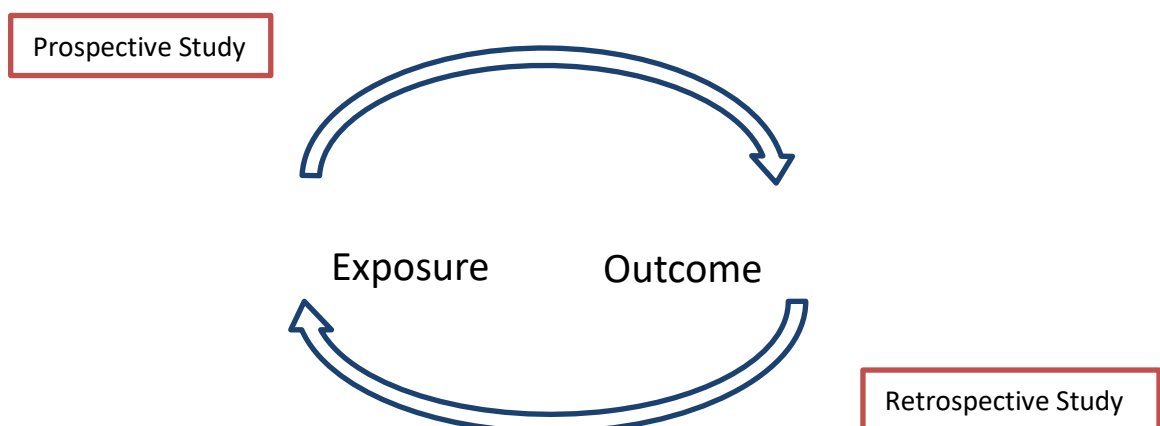
(7) These six main Real World Data sources are the most often used. Besides them, plenty of sources official or not can be used: Pharmacy data, Mortality Registries, Social Media, Consumer Data gathered through devices and health applications; Laboratories tests results, DNA Banks etc

2.3.2 Typology by approach

Real World Data is also often split into two groups: **Retrospective** and **Prospective** Data. Prospective and retrospective are two different angles a researcher can use for a study.

Prospective study observes outcomes, such as the development of a disease, and relates this to other factors while retrospective study looks backwards and examines exposures to suspected risks in relation to an outcome that is established at the start of the study (Website “Stats Direct”).

Figure 2.1: Prospective and Retrospective Studies



Source: Text above

Table 2.2: Main differences between Retrospective and Prospective study

Retrospective	Prospective
Looks backwards	From present time to future
The outcome has already happened by the time of study design (ex: pulmonary cancer)	The outcome has not yet happened
Can only be observational	Can be observational or interventional
Data already available	Collection of data is necessary

Source: Inspired by the table found in the Medical Biostatistics website; <http://bit.ly/2v9715t>

2.4 Advantages and drawbacks of RWE comparing to RCTs

RWE shows some incontestable positive outcomes that are impossible or hard to get with RCTs. The ISPOR Task Force Report on RWE in payment decisions listed some of the benefits of this new kind of data:

“Estimates of effectiveness rather than efficacy in a variety of typical practice settings”

“Data in situations where it is not possible to conduct an RCT”

In some situation, it is legally, ethically or physically impossible to conduct a RCT, for example in situation of narcotic abuse.

“Information on how a product is dosed and applied in clinical practice and on levels of compliance and adherence to therapy”

In RCTs patients are pre-selected according to the disease the searchers want to study. All patients receive a very exact number of drugs. Everything is controlled and nothing is being missed. In real life, patients can combine more than one disease, and so more than one treatment. For example, diabetes and cholesterol are often co-diseases. It is then important to verify than one treatment does not interfere with the other one.

In real life patients can also have a lower adherence (whether the patient takes his treatment as prescribed) than in clinical trials. It is therefore important to check if the treatment is working with an adherence less than 100%. For example, a 95% of adherence

is requested for antiretroviral therapy against VIH to be effective (Basavaprabhu et al, 2013).

“Estimates of the evolving risk-benefit profile of a new intervention, including long-term (and rare) clinical benefits and harms”

While RCTs are done in a short time, RWE can ensure a lifelong follow-up, for example the Electronic Health Record or the Patient Registries. For example, the Cystic Fibrosis Patient Registry has been created in 1966 and is collecting data on health outcomes, clinical care and demographic characteristics (Cystic Fibrosis Foundation Website). It has nowadays data about 28,000 people with Cystic Fibrosis on decades. Much more people or time than a RCT could do. As it is impossible to conduct a RCT on an entire human life, we never know the real risk of a drug on a human life. RWE can provide this kind of data and help to estimate the safety profile of each drug in long term.

“Examination of clinical outcomes in a diverse study population that reflects the range and distribution of patients observed in clinical practice”

RCTs are done in a small amount of people. RWE can be done in much bigger amount of people giving more strength to the results.

“Results on a broader range of outcomes (well-being, quality of life), than have traditionally been collected in RCTs (major morbidity, short-term mortality)”

Some outcomes as the well-being are hard to catch in RCTs. Patient Reported Outcomes (PROs) as questionnaires or interviews are essential for catching feelings and sensations.

Additionally, in some disease, the survival rate doesn't make sense; the Quality of Life is the main goal, for example the Atopic Dermatitis. The death rate is very low, but the disease burden is very high in term of quality of life. PROs provide essential information on the impact of this disease on people's life.

“Data in circumstances where there is an urgency to provide reimbursement for some therapies because it is the only therapy available and may be life-saving”

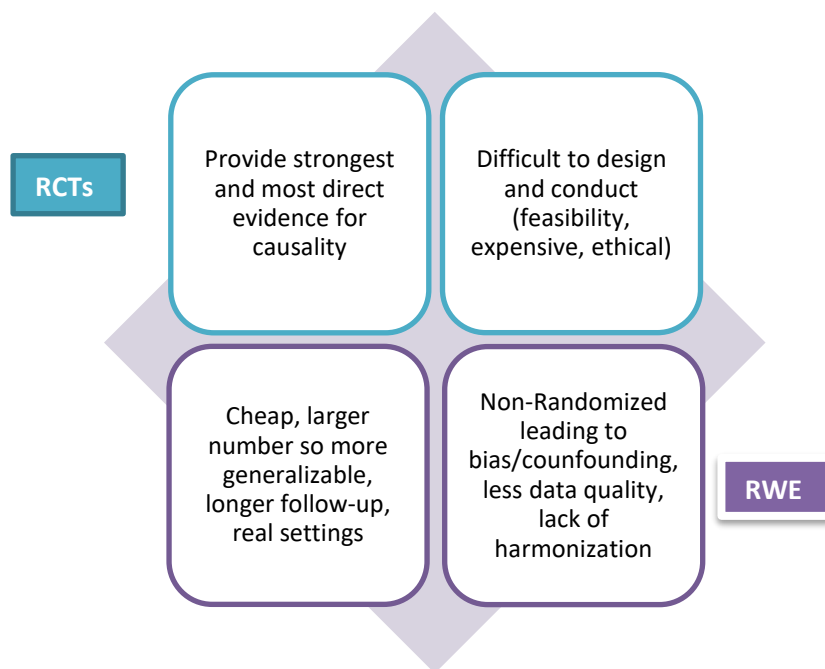
Rare Diseases are very problematic in evidence generation as the range of people who can be selected for RCT is very narrow. “A disease or disorder is defined as rare in Europe when it affects less than 1 in 2000” (Rare Disease Day Organization Website).

Additionally, the high number of children in rare diseases is causing a problem as it is typically a sub-population excluded from RCT for ethical reason, “50% of rare diseases touch children” (Rare Disease Day Organization Website).

RWE as Patient Registries can face better these limitations and complement RCTs in difficult situations. Gliklich in his article published in 2012 in the ISPOR Journal states that RWE as patient registries “are not a substitution for controlled trials. Instead, they serve as a valuable tool for researchers when determining if a trial is feasible and can complement a trial by providing data on product use, treatment patterns, and clinical questions about the disease that most likely do not already exist” RWE can help to fasten the gathering of evidence in situations where time is life-saving as no therapies exist.

RWE is using a larger amount of heterogeneous people; it is a big advantage but also a drawback. Non-randomized selection exposes the study to bias and confounding (Saturni et al, 2014). Data collected from RWE sources is also more likely to be incomplete and of poorer quality. Indeed, they are mostly not collected for research purposes and the data extraction is not as controlled as in RCTs. Additionally, RWE is suffering of a lack of harmonization: Patient Registries, Electronic Health Records, Biobanks, Surveys, Interviews etc. RWE has a lot of sources in different format making it hard to structure.

Figure 2.2: Sum up of the advantages and drawbacks of RCTs and RWE



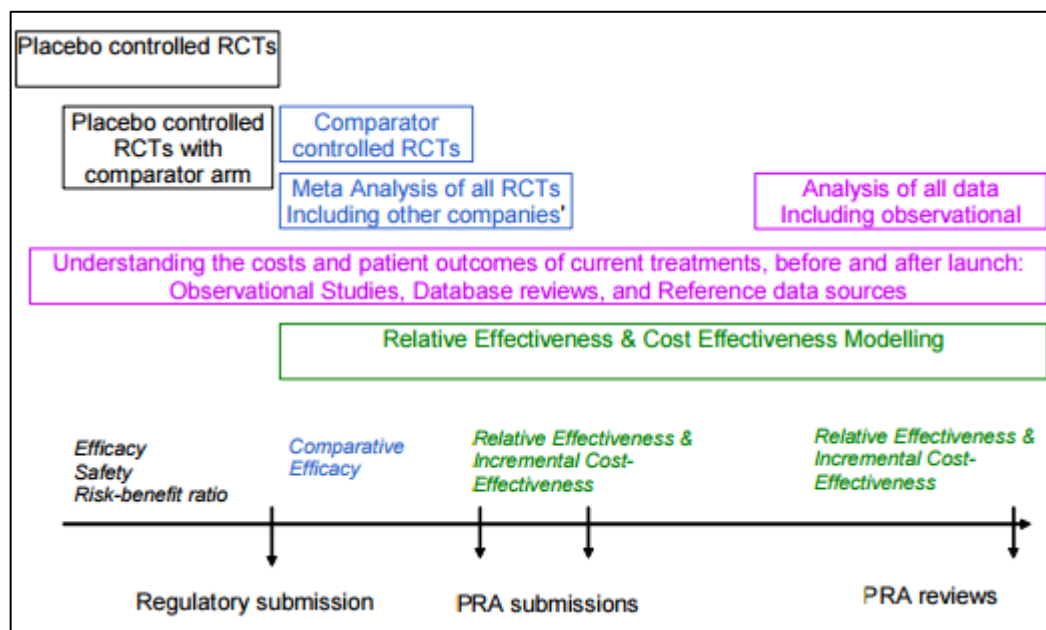
Source: Sum up of info and sources above

By looking at the pros and cons of each method, a clear complementarity appears. RCTs and RWE can be used together as Cox, 2013 suggested: “Each approach (RCTs, prospective observational and retrospective database studies) has unique strengths and weaknesses. By using a combination of these approaches and leveraging the ability to supplement any missing information with existing data from routine sources such as EHR, researchers can fill evidence gaps more efficiently and effectively.” RWE can also be a second step, as a confirmation of results found with RCTs as Saturni et al, 2014, is proposing “a workflow in which results from RCTs need to be confirmed by real life studies”.

2.5 The present use of RWE

The balance between RCTs and RWE swings from RCTs dominance at initial market authorization to a much greater use of RWE post-authorization (European Commission, 2016). This shift follows the evidence need moving from efficacy-evidence at the drug development to effectiveness-evidence at price and reimbursement of the drug.

Figure 2.3: Evidence needs evolves over time



*PRA= Price Reimbursement Access

Source: Cone et al, 2008, Regulation Reimbursement and Two sides of the same coin?

Efficacy-Evidence

Each drug goes through a regulatory submission for getting the Market Authorization. According to the online glossary of the World Health Organization (WHO) it is “an official document issued by the competent drug regulatory authority for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality”. As regulatory approval is based on efficacy, safety, and quality, at this step RCTs are the most appropriate methodology, showing if the drug works and does more good than harm in optimum conditions.

Effectiveness-Evidence

After getting the market authorization, drugs are assessed for price and reimbursement. Wide system differences exist between countries but in the last decades a tendency has been clearly identified: the growing role of the Health Technology Assessment (HTA). In contrast to regulatory approval, Health Technology Assessment examines the global impact of a drug.

According to the World Health Organization (WHO), HTA “refers to the systematic evaluation of properties, effects, and/or impacts of health technology. It is a multidisciplinary process to evaluate the social, economic, organizational and ethical issues of a health intervention or health technology. The main purpose of conducting an assessment is to inform a policy decision making.”

These last decades, HTA systems spread worldwide and got a better structure. The International Network of Agencies for Health Technology Assessment (INAHTA) was created in 1993 and counts nowadays 55 member’s agencies from 32 countries (INAHTA website). There are wide differences of drug appraisal between each country, especially on the economic factors, nevertheless all HTA agencies are relying on the same pillar: the evidence-based decision. Every HTA recommendation is based on the evidences raised by the evaluation of the data provided on the drug. The correct use of data is crucial for a good assessment of the drugs, it is consequently advocated as one of their top missions: “All INAHTA members assess health technologies to support evidence based decision making in national or regional health systems” (INAHTA Website).

Even though RCTs remain the gold standard in HTA decisions, nowadays a significant proportion of price and reimbursement submissions of new drugs are composed of RWE. At this time of the process, the efficacy of the drug is already proven. A good price and reimbursement is given to drugs showing a good effectiveness. With the rise of the technology, RWE is becoming enough trustful to show some evidences from the real world, especially in the Managed Entry Agreements.

2.6 Managed Entry Agreements

Traditionally, reimbursement decisions were limited to three options: Yes, No, Yes but with restrictions (ex: on a subgroup of patients, only if the first line drug didn’t work). With the increase of drug cost, higher control of the health expenses and the global uncertainty at drug launch, new reimbursement agreements have recently appeared. And RWE is nowadays a central part of these new agreements.

At the time of making reimbursement decision, there is always a significant uncertainty. In some cases, this uncertainty is too big for allowing reimbursement. For example, a lack of effectiveness-evidence or a doubt on the budget impact for a drug. In these cases, HTA

can refuse the coverage, impose a reduce price/reimbursement or propose a more complex performance linked agreement called Managed Entry Agreements (MEA). It can also be called Risk-Sharing Agreements or Patient Access Schemes (PAS).

MEA can reduce uncertainty by sharing the risks of a drug launch. A Managed Entry Agreement is “an arrangement between a manufacturer and payer/provider that enables access to (coverage/reimbursement of) a health technology subject to specified conditions. These arrangements can use a variety of mechanisms to address uncertainty about the performance of technologies or to manage the adoption of technologies in order to maximize effective their use, or limit their budget impact” (Carlson et al, 2010).

A wide variety of MEA exist, here are some examples:

- Initial free product and then reimbursement given if the effectiveness is shown
- If performance is lower than predicted by the manufacturer, he will provide a discount to the payer
- The manufacturer will reimburse the payer the doses of patients who did not respond to the therapy
- If a bigger quantity of drug doses is sold, the excess doses will be given for free by the manufacturer

When the MEA is based on the performance of the drugs, as the three first examples, Real World Evidence is a central piece of the agreement. It will prove the real performance of the drug and therefore trigger a reimbursement or a discount. For example, Patient Registries can be conducted after the release of the drug on the market and a discount from the manufacturer to the payer is given if, after 2 years, performance objective is not achieved.

3. Methodology

3.1 Objective

The strategy of this paper is divided into two studies, one quantitative, one qualitative.

The first study focuses on how RWE is accepted in the HTA recommendations. A quick look on the HTA decisions showed that RWE is very often refused. Therefore, the study's objective is to study the reasons why RWE is often refused.

The second study is a study of three successful cases where RWE has been the crucial element that changed the HTA decision from a refusal to an agreement. The aim is to make a link between the two studies and understand why RWE is often refused and why some RWE, unlike the others, are accepted and are making the positive differences.

3.2 Selection Criteria and methodology

One of the limits of this paper is the lack of information. Data on drug HTA assessment is available on each HTA country website but data quantity and quality differs a lot between each country. For this first study, the data selected are coming from the French HTA *Haute Autorité de Santé* (HAS). Unlike Portugal, Germany or Italy HTA, HAS is giving a very consistent report for each drug's assessment and very often in English. The selection is focus on the drug's assessment published in the HAS website in the month of January. Reregistration of drugs are excluded. The study includes 25 drug's assessments. On the 25 assessments, the cases containing RWE are going to be studied deeper to find if the RWE used have been accepted. And if they have been refused, which reasons justified the refusal.

For the second study, the three cases selected are based on the article "Does real world evidence matter in Health Technology Assessments?" written by Linden et al, 2015, in the website Pharmaphorum. The three cases are cases "where a drug was not initially recommended but, in re-submissions with the addition of RWE, a positive reimbursement decision was given." This selection criteria permit to identify the impact of the RWE besides the RCTs. The cases are the following: Yervoy in Australia HTA (PBAC), Zaltrap in Scotland HTA (SMC) and Myozyme in French HTA (HAS). The article is giving a brief overview of the cases. The aim of this paper is to go far deeper in the HTA decisions.

3.3 Collection of Data

All the HTA submissions and decisions are published in their websites, here is the list and the website link to the HTA included in my studies:

- France: HAS – Haute Autorité de Santé

<http://bit.ly/2jjpdVn>

-Scotland: SMC - Scottish Medicines Consortium

<http://bit.ly/2tF4mmW>

-Australia: PBAC - Pharmaceutical Benefits Advisory Committee

<http://bit.ly/2tHWnW4>

4. Quantitative Study on RWE acceptance

A quick look to the HTA decisions showed that they often refuse RWE. This first study aims to verify this hypothesis and then analyse the reasons of HTA when they refuse a RWE in a submission. To the best of my knowledge there are no studies in the literature collecting the reasons why an HTA refused a RWE.

The first step of the study was to collect decisions of the French HTA (HAS) in the month of January 2017 (Table 4.1). The column “Decision” refers to the decision of reimbursement. Refused means that the drug won’t be registered on the reimbursement list.

Most of submissions studied were inscription which means it was the first submission of the manufacturer for this drug. Revaluation is when the manufacturer asks the HTA to reevaluate new pieces of evidence to get a better reimbursement and potential good price.

In blue, the submissions including RWE which are studied deeper in the table 4.2.

Table 4.1: HAS Decisions in January 2017

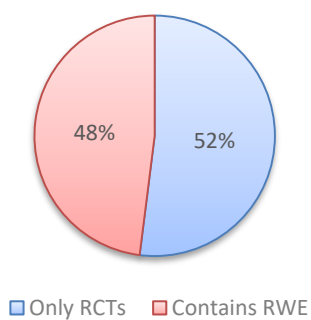
Drug	Indication	Company	Date	Type	Decision	RWE
Misodel	Pregnancy	Ferring	14/12/2016	Inscription	Refused	YES
Pradaxa	Anticoagulant	B-I	14/12/2016	Revaluation	No modification	YES
Orfadin	Orphan Disease	Biovitrum	14/12/2016	Inscription	Accepted	NO
Monover	Hematology	Medipha	14/12/2016	Inscription	Accepted	YES
Champix	Smoking Addiction	Pfizer	09/11/2016	Inscription	Accepted	YES
Jardiance	Diabetes	B-I	19/10/2016	Revaluation	No modification	YES
Briviact	Epilepsy	UCB Pharma	20/07/16	Inscription	Accepted	NO
Paracetamol	Painkiller	Mylan Pharma	11/01/2017	Inscription	Accepted	NO
Pixuvri	Hematology	Servier	13/01/17	Revaluation	No modification	YES
Likozam	Psychiatry	Advicernne	13/01/17	Inscription	Accepted	YES
Lixiana	Anticoagulant cerebrovascular stroke	Daiichi Sankyo	13/01/17	Inscription	Accepted	YES
Lixiana	Anticoagulant Thrombosis/Embolism	Daiichi Sankyo	06/07/2016	Inscription	Accepted	YES
Xarelto	Anticoagulant	Bayer	11/05/2016	Revaluation	Accepted	YES
Holoclax	Stem cell	Chiesi	20/07/2016	Inscription	Accepted	YES
Domperidone	Nausea and Vomiting	Biogaran	11/01/2017	Inscription	Both, depends on the indication	NO
Bosentan	Hypertension	Accord	11/01/2017	Inscription	Accepted	NO
Bosentan	Hypertension	Teva	11/01/2017	Inscription	Accepted	NO
Bosentan	Hypertension	Mylan Pharma	11/01/2017	Inscription	Accepted	NO
Entresto	Heart Failure	Novartis	11/01/2017	Revaluation	No modification	YES
Domperidone	Nausea and Vomiting	Biogaran	11/01/2017	Inscription	Accepted	NO
Domperidone	Nausea and Vomiting	Teva	11/01/2017	Inscription	Accepted	NO
Mikicort	Corticoids	Mayoly Splinder	11/01/2017	Inscription	Accepted	NO
Taltz	Psoriasis	Lilly	05/10/2016	Inscription	Accepted	NO
Potassium H2	Supplement	H2	25/01/2017	Inscription	Accepted	NO
Cimzia	Rheumatism	UCB Pharma	11/01/2017	Inscription	Refused	NO

Source: HAS Website <http://bit.ly/2jjpdVn>

General Statistics

General statistics show first that almost one on two submissions contains RWE, 48% of submissions has at list one RWE.

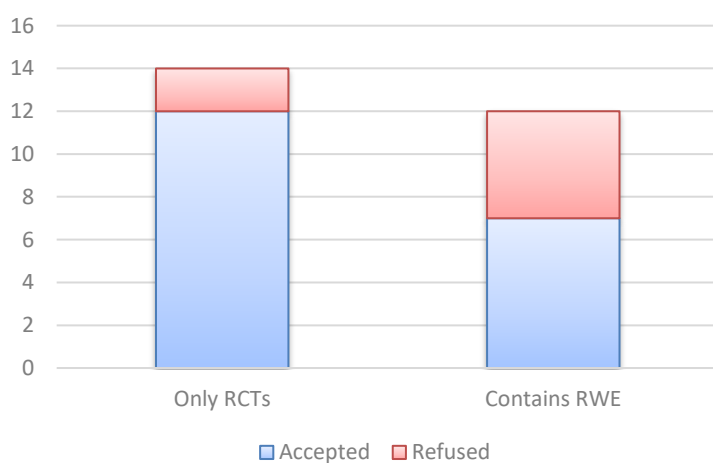
Figure 4.1: Percentage of submissions with RWE



Source: Table 4.1

Statistically submissions with RWE obtain more refusal than RCTs, 5 on 12 submissions against 2 on 14 for submissions with RCTs.

Figure 4.2: Proportion of submissions accepted or refused per the presence of RWE



Source: table 4.1

These two results demonstrate that the use of RWE is largely common among the pharmaceutical companies. Nevertheless, it is less accepted in HTA, in our case the French one, HAS. This can be explained by the role of the RCTs which still represent the “golden standard” of the evidence in drugs evaluation. RWE is a new concept which utilization is gradual in time. It is acceptable than public authorities show some limitations and doubts to use RWE.

Focus on submissions with RWE

The second step of the study is to analyse deeper the submissions including RWE from the table 4.1. The following table shows which kind of RWE were used in the submissions. It also shows if the RWE were accepted by the HTA and if not, which reasons the HTA mentioned to argue the refusal (last column “Reason”).

Table 4.2: Cases from Table 1 with RWE

Drug	Category	RWE Type	Acceptation	Reason
Misodel	Efficacy/Tolerance	Retrospective cohort from hospital patient files	NO Efficacy YES Tolerance	Doesn't study the right population The periods of study are different for the two compared drugs Bias of recommendation Selection of the patient files not well described
	Tolerance	PSUR Periodic Safety Update Report	YES	
Pradaxa	Efficacy/Tolerance	Retrospective cohort with data from SNII-RAM (Social Security data) and PMSI (Data management system)	Partially	The statistical power of the study is too weak to detect light risk increase Short term study
	Efficacy/Tolerance	Retrospective cohort with data from Medicare and Truven Health Marketscan Commercial Claims and Encounters	Partially	Lack of data on confusion factors Overestimation of some results American data with different dose and indication
	Efficacy/Tolerance	Retrospective Cohort with data from the Quebec Social Security	Partially	Lack of data Short term study, possible underestimation of risk
	Efficacy/Tolerance	Retrospective Cohort with national New-Zealand data from the NMDS (National Minimum Dataset) and Pharmaceutical	Partially	Lack of data on confusion factors
	Tolerance	National data of Pharmacovigilance 1	YES	
	Tolerance	National data of Pharmacovigilance 2	YES	
	Tolerance	International data of pharmacovigilance	Partially	Bias that could affect results
Monover	Tolerance	International data of pharmacovigilance	YES	
Champix	Tolerance	7 cohort studies	YES	
	Tolerance	National data of Pharmacovigilance	YES	
	Tolerance	Data of utilization and recommendation from IMS-EPPM	NO	Not enough quantity of recommendations for an analyze
Jardiance	Tolerance	International data of pharmacovigilance	YES	
Pixuvri	Efficacy	retrospective study	NO	The efficacy data are note available for the right indication
Likozam	Tolerance	Expanded Access Data	YES	
Lixiana	Tolerance	International data of pharmacovigilance	YES	
	Efficacy/Tolerance	Open extension study	NO	Too many patients dropped the study
Lixiana	Tolerance	International data of pharmacovigilance	YES	
Xarelto	Tolerance	National data of Pharmacovigilance	YES	
Entresto	Efficacy/Tolerance	Expanded Access Data	NO Efficacy YES Tolerance	Short term study Not enough patients High variability of the results

Source: HAS Website <http://bit.ly/2jjpdVn>

On the 25 submissions, 12 include RWE. Data on Holoclar's evaluation have been removed as this is not a typical drug but an eye transplantation it is then impossible to conduct a RCT as randomization and placebo is not possible. This paper's aim is to study the importance of RWE compared to RCTs, the case of Holoclar doesn't fit the criteria.

11 cases with RWE have been kept. The RWE provided are the following:

- 12 Cohort Studies from which 5 are retrospective. The retrospective cohorts are based on hospitals, national files and social security data as the Quebec Social Security Data, Medicare or New-Zealand data from the NMDS (National Minimum Dataset).
- 9 National & International data of Pharmacovigilance
- 3 Expanded Access Data
- 1 Data of utilization and recommendations
- 1 observational retrospective study
- 1 Expansion study

On the 27 RWE provided, 14 are given to only prove the good tolerance of the drug and 2 of them the good efficacy. 5 are given to prove both efficacy and tolerance. And two cases, Misodel and Entresto, have one RWE which is given to prove efficacy and tolerance but studied separately.

Table 4.3: Acceptation of the RWE according to the Efficacy and Tolerance category of evidence

	Accepted	Refused	Partially*	Total
Efficacy	0	1	0	1
Tolerance	17	1	1	19
Efficacy/Tolerance	0	1	4	5
Total	17	3	5	25**

Source: Table 4.2

*Partially accepted means that the HAS took the evidence in consideration but some fundamental limits to the evidence are existing

**The result doesn't count the Misodel and Entresto specific case, described below

Table 4.4: Misodel and Entresto specific cases

Drug	RWE	Category of evidence	Acceptation
Misodel	Retrospective cohort from hospital patient files	Efficacy	NO
		Tolerance	YES
Entresto	Expanded Access Data	Efficacy	NO
		Tolerance	YES

Source: Table 4.2

The table 4.3 show that most RWE are accepted in the evaluation of the HTA, 17 on 25. But a closer look demonstrate that this result is totally different when comparing the score of acceptance by tolerance and efficacy. The 17 RWE accepted were all used to prove the tolerance of the drug. The unique RWE used to prove the efficacy of the drug was refused. And the 5 RWE proving both tolerance and efficacy were refused in one case and partially in the 4 others.

Numbers are clearly demonstrating that RWE are accepted to prove tolerance but not efficacy. It is even more distinct in the table 4.4; in the case of Misodel and Entresto, the RWE used to prove both efficacy and tolerance. They were accepted for the evaluation of tolerance but refused for efficacy.

On the 10 RWE refused or partially accepted, the reasons can be sorted into three groups:

Problem of Focus

- The study is not focusing on the population related to the drug inscription (2 times)
- The period of study is different for the two compared drugs
- Transposition impossible, the data come from USA where the doses and recommendations are different compared to France

Lack of information

- Selection of the patient files not well described
- Lack of data (3 times)
- Not enough elements for an analyse

- Not enough patients/Too many patients dropped the study

Modification of the results

- Bias are existing in the study (2 times)
- The statistical power of the study is too weak to detect light risk increase
- The term of the study is too short (2 times)
- High variability of the results
- Overestimation of the results

Conclusion of the results

Results clearly show that RWE is not overcoming RCTs. While RWE is accepted when proving tolerance, it is mainly refused when proving the efficacy of a drug. The reasons mentioned by the HTA to explain the refusal are all linked to the lack of rigor of RWE:

-**The problem of focus** can be explained by the fact that RWE is suffering of a lack of harmonization: Patient Registries, Electronic Health Records, biobanks, Surveys, Interviews etc. RWE has a lot of sources in different format making it hard to structure.

-**The lack of information** can be explained by the fact that RWE is mostly not collected for research purposed and the data extraction is not as controlled as in RCTs. So, it is more likely to be incomplete and of poorer quality.

-**The modification of the results** can be explained by the fact that RWE is using a larger amount of heterogeneous people and is not randomized which expose the study to bias and confounding.

5. Case studies

5.1. Introduction

The three cases selected are based on the article “Does real world evidence matter in Health Technology Assessments?” from Liden et al, January 2015 in the website Pharmaphorum. The three cases are cases “where a drug was not initially recommended but, in re-submissions with the addition of RWE, a positive reimbursement decision was given”. This selection criteria allows to identify the impact of the RWE besides the RCTs.

The cases are the following: Yervoy in Australia HTA (PBAC), Zaltrap in Scotland HTA (SMC) and Myozyme in French HTA (HAS). While the article is giving a very brief overview of the cases, the aim of this paper is to go far deeper in the HTA decisions.

HTA systems are different among the world. Australian HTA, PBAC, and Scottish HTA, SMC, are both basing their recommendations on a clinical and economic evaluation. The economic evaluation is in both HTA based on the Quality Adjusted Life Year (QALY) system described in the following pages in the section 5.2.1. While the French HTA, HAS, has a different system based on the admitted level of the Medical Benefit (SMR- Service Médical Rendu) and Improvement of Medical Benefit (ASMR- Amélioration du Service Médical Rendu) explained in the section 5.2.2.

Table 5.1: Main info on the three cases chosen

	Case 1	Case 2	Case 3
Brand Name/INN*	Yervoy/Ipilimumab	Zaltrap/Aflibercept	Myozyme/ Alglucosidase Alfa
HTA	PBAC	SMC	HAS
Country	Australia	Scotland	France
Number of Re-submission	2	1	3
Causes of Refusal	Uncertain extent of clinical benefit, uncertain clinical place of therapy, high and uncertain cost-effectiveness ratio and uncertain financial costs	Weakness of the economic case	Not enough data on the effectiveness of the drug
RWE used	Periodic Safety Update Report & data from Patient Access Programs	Two on-going, open-label, single-arm studies	Observational studies, Pompe disease registry
Discount provided	YES	YES	Unknown
Managed Entry Agreements	Cost-effectiveness or budget impact	Unknown	Unknown

Source: All the information from this table have been found in the website of PBAC, SMC and HAS

- France: HAS – Haute Autorité de Santé

<http://bit.ly/2jjpdVn>

-Scotland: SMC - Scottish Medicines Consortium

<http://bit.ly/2tF4mmW>

-Australia: PBAC - Pharmaceutical Benefits Advisory Committee

<http://bit.ly/2tHWnW4>

*International Nonproprietary Name

5.2. Systems of evaluation

5.2.1. The QALY system

QALY stands for Quality Adjusted Life Year. “It is a tool used in health economics evaluation to quantify the health effect of a medical intervention” (Lieven, 2017). A QALY considers how a treatment affects a patient’s quantity of life and quality of life. The quality of life is indicated on a range between 1 and 0; 1 is the maximum and means perfect health and 0 is the minimum and means death. The calculation is the following:

$$\text{Years of Life} \times \text{Quality of Life} = \text{QALYs}$$

Considering the calculation, here are some example:

- A person who lives one year in perfect health will have 1 QALY:

$$1 \text{ Year of Life} \times 1 \text{ Perfect Quality of Life} = 1 \text{ QALY}$$

- A person who lives only for half a year but in perfect health will have 0.5 QALYs:

$$0.5 \text{ Years of Life} \times 1 \text{ Perfect Quality of Life} = 0.5 \text{ QALYs}$$

- In the same logic, if a person lives for one year in a situation with half of perfect health, that person will also have 0.5 QALYs:

$$1 \text{ Year of Life} \times 0.5 \text{ Medium Quality of Life} = 0.5 \text{ QALYs}$$

QALYs is used to measure and compare the cost-effectiveness of each medicine. States have a limited amount of budget, they can’t pay for all drugs. The QALYs is a tool which help to take decisions on which medicine would contribute the most to the well-being of the society taking into consideration the cost and the benefits of each drug.

This system is used by several countries for drug assessment and price and reimbursement settings as Scotland or Australia which are respectively our first and second cases.

5.2.2. The SMR/ASMR system

The SMR/ASMR is a unique system only used in France.

For each submission the French HTA, HAS, takes into consideration all the evidences on the drugs and informs the admitted level of the Medical Benefit (SMR- Service Médical Rendu) and the admitted level Improvement of Medical Benefit (ASMR- Amélioration du Service Médical Rendu) (Chicoye et al, 2009).

SMR and ASMR can be seen as two ladders of marks.

The SMR has four levels and shows the importance of the medical benefit of the drug: insufficient, weak, moderate or important. It determines the stage of reimbursement: 15% for a weak SMR, 30% for moderate and 65% for important (HAS Website, Évaluation des médicaments en vue de leur remboursement, 2015).

The ASMR is a crucial element for the determination of the price. It has 5 levels:

- Level I, Major innovation
- Level II, Important improvement
- Level III, Significant improvement
- Level IV, Minor improvement
- Level V, No improvement

The price of the drug will be partially determined by the ASMR level.

5.3. Cases studied

5.3.1. Yervoy (Australia)

5.3.1.1. Drug Details

Brand Name/ International Non-proprietary Name(INN): Yervoy/Ipilimumab

Category: Malignant Melanoma (Skin Cancer)

Submission: July 2011

Reason of refusal: uncertain extent of clinical benefit, uncertain clinical place of therapy, high and uncertain cost-effectiveness ratio and uncertain financial costs

Re-Submission: March 2012

Re-submission n°2: November 2012

HTA: Pharmaceutical Benefits Advisory Committee (PBAC)

Manufacturer: Bristol-Myers Squibb

The information for this case study have been found in the public reports provided by the PBAC in their website. The reports are available from:

- Submission: <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2011-07/pbac-psd-ipilimumab-july11>
- Re-submission n°1: <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2012-03/ipilimumab>
- Re-submission n°2: <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2012-11/ipilimumab>

According to the Dermatology Information System DermIS the malignant melanoma is “the most aggressive and life-threatening skin cancer. It develops in the cells that give the skin its color (melanocytes) and has a very high tendency to spread to other parts of the body”.



Source : <https://www.ilmelanoma.com/en/melanoma/m>

According to the PBAC, advanced melanoma “has a median survival of approximately 6 to 9 months”. The strongest environmental risk factor in the development of melanoma is the exposure to strong solar UV radiation. Australia has the highest incidence of advanced melanoma per population in the world due to a very strong solar situation and a high presence of Caucasian population.

Ipilimumab is a treatment for patients with a such advanced stage of malignant melanoma that surgery is impossible, and who were not responsive or were intolerant to prior therapy.

5.3.1.2. Clinical Analysis

The submission presented a randomised double-blind, multicentre trial subjects with advanced stage of melanoma, impossible to operate, and who were not responsive or unable to tolerate at least one or more previous treatments. The result of the study was a reduction in hazard of death of 34% in the ipilimumab monotherapy group compared to the control group. The median survival for the ipilimumab monotherapy arm was 10.12 months compared to 6.44 months in the control group. The PBAC noted that the median difference in survival was approximately 3.6 months. The PBAC considered these results were “uncertain and difficult to interpret due to the low number of patients remaining in the study”. Especially because ipilimumab treatment is very heavy; some patients had to stop the study because of adverse events. “Approximately 62% of patients in the ipilimumab monotherapy group compared to 32% of patients in the control group experienced an Immune Related Adverse Events (irAE)” according to the PBAC report. This represents a statistically significant difference.

5.3.1.3. Economic Analysis

The base case incremental cost per QALY gained was between \$105,000 and \$200,000 and the estimated financial cost to the PBS was considered to be between \$30-60 million in Year 5.

5.3.1.4. Recommendation

The PBAC acknowledged that there was “a high clinical need for a drug to treat metastatic melanoma as there are few other viable options for patients with this condition”.

The submission described ipilimumab as “superior in terms of comparative effectiveness” but the PBAC considered this claim may not be reasonable as ipilimumab may be considered “inferior in terms of immune related adverse events”. Moreover, a recent publication showed an incremental benefit of 2.1 months. The PBAC therefore concluded that the 3.6 months survival gain was an overestimate.

The PBAC considered that the costs associated with the treatment adverse drug effects were considerably underestimated as there may be more inpatient hospital cost as well as greater costs associated with the PBS subsidised treatment of adverse events.

There is also potential for use in the first-line setting, even if the listing mandates failure of a first line systemic therapy. Physicians still have the freedom to use the drug in first line. The consequence will be an increase of the budget allocated to this treatment.

The PBAC therefore refused the reimbursement because of an “uncertain extent of clinical benefit, uncertain clinical place of therapy, high and uncertain cost-effectiveness ratio and uncertain financial costs.”

5.3.1.5. Re-Submission

In the first re-submission, there were no additional evidences but additional exploratory analyses relating to the safety profiles of ipilimumab. The resubmission claimed that early management of irAEs can minimise their impact. The company also proposed a reduce price but the PBAC did not change its decision.

In the second re-submission, a new discount was proposed; the new proposed cost was \$45,000 - \$75,000 per QALY. The global estimated budget of the PBAC increased to more than \$100 in year 5 including because of the acceptation of the PBAC to authorize the treatment in first line if needed.

There were no new comparative clinical data but several new clinical trials related to the durability of the drug:

- Five-year follow-up from ipilimumab clinical trials
- Four-year follow-up from ipilimumab clinical trial

- Long-term (five years and greater) follow-up from 177 metastatic melanoma patients treated with ipilimumab
- The resubmission cited two additional papers outlining existing longer-term follow-up than five years
- An expert statement related to ipilimumab and durability.

And three RWE:

- The most recent Periodic Safety Update Report (PSUR)
- Italian ‘real-world’ data relating to efficacy, safety, and rates of re-induction from the European Expanded Access Programme (EAP) and submitted to the European Society for Medical Oncology (ESMO) conference in October 2012
- Australian ‘real-world’ data resulting from the Patient Access Program (which existed between the 1st August 2011 and the 15th April 2012)

The new pieces of evidence confirmed the durability of the clinical effect. The PBAC agreed that the results from the European Expanded Access Programme (EAP) in Italy supported the results seen in the other trials mentioned above. Additionally, new toxicity data from the latest Periodic Safety Update Report (PSUR) did not identify any new safety concerns. No further comments have been made on the role of the RWE.

5.3.1.6. Managed Entry Agreements

The PBAC considered that the new proposed cost of \$45,000 - \$75,000 per QALY was “high but acceptable if the modelled survival gain is observed in clinical practice”. In the last submissions, the uncertainty of the clinical benefit, of the place of the therapy and of the financial costs pushed the PBAC to refuse the treatment. The PBAC is now proposing two different MEA to reduce the risks and costs:

- The implementation of “a mechanism to verify the anticipated overall survival benefits of ipilimumab in real world clinical practice in Australia”. This mechanism should be done in a way that it gives evidences of “whether or not the extent of the survival benefit presented in the submission and which was used in the calculation of cost-effectiveness, was realised in Australian clinical practice”. The company would have to reimburse the

cost of difference in performance between the observed benefits and the benefits promised in submission.

- “Negotiation of significant rebates in terms of number of patients and dose”. Which means that the company will offer the additional treatments if the number of patients treated has been overwhelmed. This negotiation aims to control the budget decided by the PBAC for this treatment which is over \$100 million in Year 5.

The final MEA chosen remain non-public. In both cases, RWE will be collected to measure the impact of the treatment and to calculate the rebates that the company will give to the Australian healthcare system.

5.3.2. Zaltrap (Scotland)

5.3.2.1. Drug Details

Brand Name/INN: Zaltrap/Aflibercept

Category: colorectal Cancer

Submission: 7 June 2013

Reason of Refusal: Weakness of the economic case

Re-Submission: 7 February 2014

HTA: Scottish Medicines Consortium (SMC)

Manufacturer: Sanofi-Aventis



Source : <http://www.zaltrap.com>

The information for this case study have been found in the public reports provided by the SMC in their website. The reports are available from:

- Submission:
https://www.scottishmedicines.org.uk/SMC_Advice/Advice/878_13_aflibercept_Zaltrap/aflibercept_Zaltrap
- Re-submission:
https://www.scottishmedicines.org.uk/SMC_Advice/Advice/878_13_aflibercept_Zaltrap/aflibercept_Zaltrap_Resubmission

Aflibercept is a treatment for metastatic colorectal cancer. Metastatic colorectal cancer is cancer of the large bowel and rectum that has spread to other parts of the body. Aflibercept is given as an intravenous infusion over one hour every 2 weeks. It is given in combination with other chemotherapy.

5.3.2.2. Clinical Analysis

The original submission contains one evidence; a randomised, placebo-controlled study. The primary endpoint was overall survival. Results of the study show that the median overall survival was significantly longer for aflibercept than placebo. The secondary endpoints included progression free survival (PFS) and response rate. The progression free survival is defined by the National Cancer Institute as “the length of time

during and after the treatment of a disease, such as cancer, that patient lives with the disease but it does not get worse”. The PFS and response rate were both significantly higher for the aflibercept group than placebo. Better results are confirmed in some subgroups of patients, for example, patients with liver metastases.

In brief, the RCT showed a significant longer median overall survival. Results of the secondary endpoints were supportive of the primary endpoint. The comparator used and the study inclusion criteria were appropriate. But there are some limitations in the study results and design, the major ones are described below.

Even though the median overall survival is higher among patients treated with aflibercept, the additional median survival of 1.44 months is a modest result. Furthermore, there is no data on quality of life.

The treatment with aflibercept require an additional infusion of one-hour duration which means additional costs and services. Moreover, the combination of aflibercept to other chemotherapy was associated with significant adverse events that were not always manageable clinically, and forced some patients to stop the treatment.

5.3.2.3. Economic Analysis

The original cost per QALY is not communicated. Data published concerned the cost per QALY with the inclusion of a discount proposed by Sanofi. The treatment offers a 0.2429 QALY gain, for an incremental cost of £8,816 which is equivalent to the amount of £36,294 for one QALY.

For the subgroup of patients with liver metastases the cost per QALY was estimated to be £30,474 with the discount for an incremental cost of £10,974 and a QALY gain of 0.3601.

The difference in overall survival is statistically significant in the calculation. A better result in overall survival, like an increase by 30%, would have reduce the cost per QALY to 28.5K. The additional cost of the aflibercept treatment was not included in the QALY calculation.

5.3.2.4. Recommendation

The reimbursement of aflibercept was refused because the “economic case has not been demonstrated”, indeed the high cost per QALY and the weaknesses outlined above didn’t convince the SMC.

5.3.2.5. Re-submission

In the re-submission, the company provided a deeper analysis of the randomised controlled study showed in the submission and, above all, two RWE. Two on-going, open-label, single-arm studies aiming to assess the safety and quality of life of the aflibercept treatment. The inclusion and exclusion criteria were similar to the randomised controlled study. Five dimensions were included in the study (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and then converted into a single index utility score (minimum value of -0.594 and a maximum value of 1.0). At baseline the mean of the utility score was 0.77 and at cycle three it was 0.78. At cycle five the utility score was 0.79. The utility score showed that the quality of life under the treatment is overall good, and remain stable.

A revised discount was submitted by the company and accepted. With the discount, the submitting company estimated a cost per QALY of £34,623 based on an incremental cost of £8,519 and a QALY gain of 0.2460. For the subgroup of patients with liver metastases the cost per QALY was estimated at £27,424 based on an incremental cost of £10,164 and a QALY gain 0.3706.

Table 5.2: QALY gain and cost difference between the submission and the resubmission

	Submission		Resubmission	
	Overall	Subgroup	Overall	Subgroup
QALY gain	0.2429	0.3601	0.2460	0.3706
Incremental Cost £	8,816	10,974	8,519	10,164
Cost per QALY £	36,294	30,474	34,623	27,424

Source: Public reports of the submission and re-submission, available in SMC Website and quoted above

In the resubmission, the QALY gain slightly increased, especially thanks to the two open studies which proved a stable quality of life under the treatment. Additionally, the

incremental cost decreased because of a bigger discount from the company. In consequence, the cost per QALY decreased. But the SMC announced that this decrease is largely due to the increase of the discount.

The SMC affirms that it does not have a formal threshold cost per QALY below which cost-effectiveness would be considered demonstrated. When the cost per QALY is high, other factors can also play a role in SMC's assessment and may change the final decision.

These factors are listed in the SMC website and are the following:

- "Evidence of a substantial improvement in life expectancy with a sufficient quality of life to make the extra survival desirable. Substantial improvement in life expectancy would normally be a median gain of 3 months.
- Evidence of a substantial improvement in quality of life (with or without survival benefit);
- Evidence that a sub-group of patients may derive specific or extra benefit and that the medicine in question can, in practice, be targeted at this sub-group;
- Absence of other therapeutic options of proven benefit for the disease in question
- Possible bridging to another definitive therapy in a defined proportion of patients;"

In the Zaltrap case, the SMC agreed that the criteria of a substantial improvement in quality of life in the patient population targeted in the submission was satisfied and there being a subgroup of patients who may derive specific or extra benefit were satisfied. **Therefore, the high cost per QALY is considered acceptable given the reasons described just above.**

5.3.3. Myozyme (France)

5.3.3.1. Drug Details

Brand Name/ International Non-proprietary Name (INN): Myozyme/ Alglucosidase Alfa

Category: Pompe disease

Submission: September 2006

Reason of refusal: Lack of data on effectiveness

Re-submission: June 2010

Re-submission: January 2013

Re-submission: March 2017

HTA: Haute Autorité de Santé (HAS)

Manufacturer: Genzyme



Source : <https://www.alux.com/most-expensive-drug>

The information for this case study have been found in the public reports provided by the HAS in their website. The reports are available from:

- Submission: https://www.has-sante.fr/portail/jcms/c_446700/en/myozyme
- Re-submission N°1: https://www.has-sante.fr/portail/jcms/c_967981/en/myozyme
- Re-submission N°2: https://www.has-sante.fr/portail/jcms/c_1359745/en/myozyme
- Re-submission N°3: https://www.has-sante.fr/portail/jcms/c_2754216/fr/myozyme

According to the Genetics Home Reference website “the Pompe disease is an inherited disorder caused by the build-up of a complex sugar called glycogen in the body's cells. The accumulation of glycogen in certain organs and tissues, especially muscles, impairs their ability to function normally.”

According to the report submitted by Genzyme to the HAS there are two forms of Pompe disease:

- “The classic form of infantile-onset Pompe disease begins within a few months of birth. Infants with this disorder typically experience muscle weakness (myopathy), poor muscle tone (hypotonia), an enlarged liver (hepatomegaly), and heart defects. Affected infants may also fail to gain weight and grow at the expected rate (failure to thrive) and have breathing problems. If untreated, this form of Pompe disease leads to death from heart failure in the first year of life.”
- “The late-onset type of Pompe disease may not become apparent until later in childhood, adolescence, or adulthood. Most individuals with late-onset Pompe disease experience progressive muscle weakness, especially in the legs and the trunk, including the muscles that control breathing. As the disorder progresses, breathing problems can lead to respiratory failure.”

Myozyme is a replacement therapy of the Alglucosidase Alfa enzyme. It obtained the market authorization in 2006 for the two clinical groups, the infantile and the late-onset. It is the first drug to treat this disease. The Pompe disease is a rare disease, according to the HAS its frequency is “one suffering person on 138 000 people”. In total nowadays, the target population of Myozyme is about “170 people from which around 20 are the infantile clinical form of the disease”.

5.3.3.2. Submission:

In its first submission Genzyme provided three randomized controlled trials. Two for the infantile form, and one for the late one.

The main criteria of the infantile-onset studies was the survival rate while the second criteria were various as the growth and improvement of the cerebral capacity, the survival rate without respiratory aid or the decrease of the left ventricular mass. In the first study, the survival rate was 100% after 18 months and patients showed a clear improvement of their cerebral capacity. The second study got a survival rate of 73% after 52 weeks and similar benefits on the cerebral capacity were demonstrated.

The small number of patients in the late-onset clinical trial (Five patients) and the heterogeneity of the results didn't allow any conclusions on the effectiveness of the drug. The very small number of patients in the trial is mainly due to the rarity of the Pompe disease. Genzyme also provided a RWE data from an observational study authorized in the context of an Expanded Access Program (EAP). According to the FDA (U.S Food & Drug Administration) an EAP, also called "compassionate use," is "the use outside of a clinical trial of an investigational medical product (still not approved) to patient suffering from a serious disease or condition for which there no other alternative therapy exists". The results were also to heterogeneous to make any conclusions.

The HAS granted the inscription on the reimbursement list for Myozyme to treat the infantile-onset and refused it for the late-onset because of the lack of data on the drug effectiveness in this clinical form.

5.3.3.3. Re-submission: June 2010

The re-submission focused only on the late-onset form of the disease. Genzyme delivered one randomized controlled trial and five RWE.

- The randomized controlled trial vs placebo was evaluating the global physical capacity of the patients. Results were positives for the group treated with Myozyme; the 6 minutes' walk test showed a significant improvement. Patients could walk on a bigger distance than the placebo group.
- Two prospective observational studies were refused because of the small number of patients. Their results were took into account only for the tolerance analysis of the submissions.
- An observational study studied the capacity of walking of 44 patients after a Myozyme treatment of one year. Results confirmed the randomized controlled trial. Indeed, patients could walk far longer at the end of the study.
- The French Pompe disease registry was created in 2004. An evaluation of the people suffering of Pompe disease is recommended every year, and every 6 months for patients under Myozyme treatment. On January 1st 2009, on the 75-people included in the registry, 60 of them were under Myozyme treatment. Data

collected from the registry showed a quite variability among the patients. But a stability or an improvement of physical capacity is seen for 2/3 of the patients.

- The international Pompe disease registry started in 2004 includes in October 2008 564 patients from the country where Myozyme got the market authorization; France and USA. Data were not correctly collected along time, therefore the data were not accepted.

For its decision HAS considered the following features: the gravity of the disease, the lack of alternative treatment, the low undesirable effects of Myozyme and its effectiveness to stabilize or improve the physical capacity of patients. HAS regretted the lack of data on the morbidity and on the quality of life. Moreover, data in long term are missing. **HAS observed that the effectiveness of the treatment is limited but the gravity of the disease, the lack of alternative treatment and the low undesirable effects of Myozyme granted it on the inscription list for reimbursement. HAS gave a weak SMR (Service Médical Rendu – Medical benefits) which is equivalent to the first level of reimbursement allowing Myozyme to get a reimbursement of 15% and an ASMR V.**

The HAS insisted on the importance of the Pompe disease registry. They recommended a regular evaluation of the patients under treatment in order to be able to re-evaluate later the long-term effectiveness of Myozyme.

5.3.3.4. Re-submission: January 2013 and March 2017

Two other resubmissions happened in the last years in order to reevaluate the SMR/ASMR of Myozyme to get a better price and reimbursement. New data were collected, both RCTs and RWE, as retrospective studies and data from the French Pompe disease registry. The resubmission of January 2013 was a revaluation of the effectiveness of Myozyme for the late-onset clinical form only. No further effectiveness effects were shown and the SMR remained weak and the ASMR level 1.

The resubmission of March 2017 also concerned the late-onset form but also the infantile one. The evidences were mainly clinical trials, RCTs an RWE, as retrospective studies and data from the registry. Long term data didn't show good results in the late-onset patients. Myozyme procures good results on short term on the global physical capacity of the late-onset patients but in long term there are no change on the survival rate or on the progress of the disease. The new data didn't change the SMR/ASMR in both indications.

5.4. Results & Conclusions

Results of the cases are mixed in that it is impossible to conclude in any of the three cases that the RWE made just by itself changed the HTA decision.

The modification of the HTA decision for a better price or/and reimbursement always came with at least one or more of the following elements: a discount, a Managed Entry Agreements or a RCT.

Resubmission of the case 1: RWE + RCT + Discount + MEA

Resubmission of the case 2: RWE + Discount

Resubmission of the case 3: RWE + RCTs

Table 5.3: Key elements which changed the HTA decision

	Case 1: Yervoy	Case 2: Zaltrap	Case 3: Myozyme
RWE			
Discount			
MEA			
RCTs			

Source: Information described above in the case studies

In submission, it is impossible that a manufacturer brings only RWE. RCTs remain the gold standard. Nevertheless, in re-submission it is different. For example, in case 2 Yervoy, no new RCT were presented. Effectiveness was already proven; the problem was in the economic analysis. A combination of RWE and discount succeed to change the HTA decision. While in submission the role of RWE is to support RCTs, it seems that in re-submission its role are more various:

5.4.1. Market Access

RWE's role is confirmed in Managed Entry Agreements as in the case 1 of Yervoy. When the price of a drug is very high and the results on effectiveness were variable, there is a risk on the cost effectiveness of the drug. The MEA as the one of Yervoy can fill in the potential budget gap by paying the cost of difference in performance between the

observed benefits and the benefits presented in the submission. In this case RWE is the indicator to measure the performance and so determine the potential rebate. MEA combined with RWE are a key tool to improve the market access of a drug.

5.4.2. Long-term follow-up

RWE's biggest advantage is its possible long duration in comparison with a RCT. When long-term effectiveness can't be proven with RCTs, RWE can take over and provide some months or years later the pieces of long-term evidences. HAS clearly confirmed its interest in the disease registries in order to follow-up the long-term effectiveness of drugs and potentially change the price and reimbursement some years after the first submission.

A typical strategy in Market Access Business Unit is to prepare, since the start, a drug for two or more indications but to obtain the reimbursement and price at different moment. Some indications can take more times to prove effectiveness while others show a particular interest to access the market first taking into consideration the competitors pipelines. In this case RWE can be integrated, since the start, in the strategy of long-term follow-up for a specific indication which has different market access needs.

5.4.3. QALY Calculation

In the case 2 of Zaltrap in Scotland, the SMC said explicitly that the decrease of the price per QALY was mainly due to the discount than the RWE. Nevertheless, the RWE succeed to slightly increase the QALY gain and so contributed to the decrease of the cost per QALY. In cost-effectiveness model with QALY calculation RWE can weigh in the scale by influencing either the quantity of life gained or the quality of life improvement. The quantity of life gained can be proved by long-term RWE as registries while the quality of life can be demonstrated with surveys as the two questionnaire used in the case 2 of Zaltrap.

6. Conclusion

This paper approached the positive impact of RWE on the HTA price and reimbursement submissions. The first study examined one full month of submissions from the French HTA (HAS) in order to measure the degree of acceptance of RWE in HTA submissions and the reasons why the HTAs could refuse RWE. While the second study analysed three cases of resubmissions where RWE did change the HTA decisions into a positive recommendation.

In the first study, results showed that RWE were accepted by HAS when proving tolerance of the drug but refused when proving efficacy. Reasons of refusal are reflecting the lack of rigor of RWE and can be gathered into three groups: **(1)** Problem of focus (different population, period or geographical zone into a same study or comparing to the placebo group), **(2)** lack of information (data missing or not well described, too much patients dropping the study) and **(3)** modification of the results (existing bias, weak statistical power, overestimation or high variability of results). Results of the second study are mixed and complex, in that RWE does show a positive impact but this impact is limited and hard to measure. Indeed, it appeared that in the three cases RWE did not change the HTA decision only by itself. The modification of the HTA decision were always a combination of RWE with one or more of the following elements: a discount, a Managed Entry Agreements or a RCT.

To the best of my knowledge, my paper is the first study to examine and collect HTAs reasons to refuse RWE. The results of the first study of my paper prove that RWE is not overcoming RCTs. The lack of rigor, already explained in the literature, is confirmed as the big weakness of RWE. It seems completely impossible that in the future manufacturers could only bring a RWE to an HTA submission. The rigor of RCTs remain the gold standard. Nevertheless, the three case studies showed that the impact of RWE is bigger in resubmission. When RCTs failed to prove a positive economic case, a long-term efficacy or an important efficacy risk, RWE brought, in combination with discount or MEA, the missing piece of evidence. These results are consistent with the article of Liden et al (2015) which conclusions were similar. However, my case studies are far more described and analysed, which is bringing to the actual literature a more complete and detailed picture of the impact of RWE. **While the role of RWE is very often described**

in the literature as a support to RCTs, I would rather conclude that its main impactful role is to fill the “evidence gap” when RCTs failed to bring it.

As said previously, I’m convinced that RWE won’t overcome RCTs but I think that the role of RWE in HTA recommendations will increase. My job in a big pharma company in the market access division showed me that manufacturers are investing in RWE. Their biggest challenge is to increase the rigor of RWE by improving the reliability of the data and standardize the process of real world data collection. The second challenge is to integrate RWE in the early molecule development strategy by analysing where RCTs will have difficulties to bring good evidence and so prepare in advance the RWE that will fill the evidence gap. This early RCTs/RWE complementary strategy is not already implemented in pharma companies. One action to take could be to work closely with patient registries in order to help them to collect reliable and standardized data.

6. References

- Association of the British Pharmaceutical Industry (ABPI) (2011) “Demonstrating Value with Real World Data: A practical guide”, May, available from: <http://bit.ly/2vSzT2l>
- Basavaprabhu, Achappa; Madi, Deepak; Bhaskaran, Unnikrishnan; Ramapuram, John; Rao, Satish; Mahalingam, Soundarya (2013) “Adherence to antiretroviral therapy among people living with HIV”, *North American: Journal of Medical Sciences* 5 (3): 220-223.
- Beevers D. G; Lee, K. W. and Lip, G. Y. H. (2003) “The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT): ALL predictable and no big surprise out of a HAT?”, *Journal of Human Hypertension* 17, 367–372.
- Burns, Patricia; Rohrich, Rod J and Chung, Kevin (2011) “The Levels of Evidence and their role in Evidence-Based Medicine”, *Plast Reconstr Surg*; 128(1): 305–310.
- Carlson, John; Sullivan, Sean; Garrison, Louis; Veenstra, David (2010) “Linking payment to health outcomes: A taxonomy and examination of performance-based reimbursement schemes between healthcare payers and manufacturers” *Health Policy* 96(3):179-90
- Chicoye, Annie; Chhabra, Amit (2009) “Global Health Technology Assessment Road Maps”, ISPOR, October, available at: <https://www.ispor.org/HTARoadMaps/France.asp>
- Cone, Margaret; Lisinski, Tracy (2008) “Regulation and Reimbursement Two sides of the same coin?”, Workshop Report, January, Institute for Regulatory Science.
- Cochrane A.L (1972) *Effectiveness and Efficiency, Random reflections on health services*, Nuffield Provincial Hospitals Trust: London.
- Cox, Terry (2013) “The value of real-world data in drug commercialization”, Online magazine Pharmaceutical Commerce, July, available from:

[http://pharmaceuticalcommerce.com/legal-regulatory/the-value-of-real-world - data-in-drug-commercialization/](http://pharmaceuticalcommerce.com/legal-regulatory/the-value-of-real-world-data-in-drug-commercialization/)

Cystic Fibrosis Foundation Website, Patient Registries Report (1966)

Available from : <https://www.cff.org/Research/Researcher-Resources/Patient-Registry/CF-Patient-Registry-Reports/>

DermIS.net (2017) Website, page “Malignant Melanoma - Patient Information”

available from:

http://skincancer.dermis.net/content/e04typesof/e154/e155/index_eng.html

Garrison LP. Jr; Neumann PJ; Erickson P; Marshall D; Mullins CD. (2007) “Using real-world data for coverage and payment decisions: the ISPOR Real World Data Task Force report”

Gliklich RE; Dreyer NA; Leavy M (2007) “Registries for Evaluating Patient Outcomes: A User’s Guide”

Goodman Malcolm; Digli, Sandra M (2013) “Creativity and Strategic Innovation Management”

Harrison, Davis (2016) “Real World Evidence as a driver of HTA approval: Can you afford to miss out?” SVMPharma, available from : <http://bit.ly/2wRQbKE>

Haute Autorité de Santé (HAS) Website (2015) “Évaluation des médicaments en vue de leur remboursement”, available from : <http://bit.ly/2vtFOep>

IMS Brogan report (2013) “Case Studies on Real World Evidence Impacting Payer Decisions”

International Network of Agencies for Health Technology Assessment (INAHTA) “History” page from website available from: <http://www.inahta.org/about-inahta/history/>

International Network of Agencies for Health Technology Assessment (INAHTA) “Members” page from website available from: <http://www.inahta.org/members/>

Kendall J.M (2003) “Designing a research project: randomised controlled trials and their principles”, *Emergency Medicine Journal*

- Liden, Daniel; Jaksa, Ashley; Ho, Yin (2015) “Does real world evidence matter in Health Technology Assessments?” Pharmaphorum website, available from: <http://bit.ly/2iASsGF>
- Lieven, Annemans (2017) “Do you know what a QALY is, and how to calculate it?”
Website C.E.L for Pharma: <http://bit.ly/2pA1B17>
- O'Sullivan, Amy K; Thompson, David; Drummond, Michael F. (2005) “Collection of Health-Economic Data Alongside Clinical Trials: Is There a Future for Piggyback Evaluations?” *Value in Health* Volume 8, Issue 1, Pages 67-79
- Rare Disease Day Organization, Website, page “Key Figures” available from: <http://www.rarediseaseday.org/article/what-is-a-rare-disease>
- Saha, Yashajit; Kumar, Dinesh (2015) “Real-World Evidence: A Better Life Journey for Pharmas, Payers and Patients”
- Saturni S; Bellini F; Braido F; Paggiaro P; Sanduzzi A; Scichilone N; Santus PA; Morandi L; Papi A. (2013) “Randomized controlled trials and real life studies. Approaches and methodologies: a clinical point of view.”
- Schumpeter, Joseph (1942) *Capitalism, Socialism and Democracy*, George Allen and Unwin: London
- Sibbald Bonnie (1998) “Understanding controlled trials: Why are randomized controlled trials important?” *British Medical Journal* (BMJ), 316:201
- Sujay, Jadhav (2017) “Using Real World Data to Enhance Clinical Trials” available from : <http://www.clinicalinformaticsnews.com/>
- Stats Direct “Prospective VS Retrospective Studies”, available from: <http://bit.ly/2wKdNn8>
- Thompson, David (2017) “How real-world evidence is changing the game”
BioPharmaDive Website, available from: <http://bit.ly/2xosKZl>

U.S. Food & Drug Administration (2009) “Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims” *Federal Register*, 74(35):65132-133.

World Health Organization, page “Health technology assessment” from the website available from: http://www.who.int/medical_devices/assessment/en/

World Health Organization, page “Glossary” from the website available from: <http://apps.who.int/medicinedocs/en/d/Jh1456e/16.html>